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# Little Brain–Big Brain: Summary Report

D. GRUNDY & J. D. WOOD

The second biannual Little Brain–Big Brain Symposium was held at the Inter-University Seminar House in Kansai located in the rural mountains between the Japanese cities of Kobe and Osaka, 14–16 November, 1991. The meeting was organized by Kenji Tamura, Michael Schemann and Paul Enck and with the generous sponsorship of Cilag, Germany. Timing of the meeting was designed to precede the XIIIth International Symposium on Gastrointestinal Motility held in Kobe, Japan. This reflected a tradition begun with the first Little Brain–Big Brain Symposium held in Munich, Germany before the XIIth International Symposium in Gmunden, Austria. We had the pleasure of chairing alternating sessions and co-ordinating the discussion. Below we have tried to give a flavour of the meeting by highlighting some of the topics that generated, as a politician might say, a full and frank exchange of views.

Participation was limited to 38 'young' investigators working at the leading edge of research on brain–gut interactions and the neurophysiological/neuropharmacological basis for determination of gastrointestinal function by the enteric nervous system. It is the interaction between enteric (little brain) and central (big brain) nervous systems that is reflected in the title of the meeting.

The meeting aimed to offer a forum for presentation and critical discussion of current research in nervous mechanisms of digestive function. The aim was achieved by interactive presentations on the neurophysiology of the brain regions that influence gut motor and secretory function with work on the neurophysiology of the microcircuits of the enteric nervous system and integrated responses of the effector systems that determine digestive behaviour. Each presentation consisted of a 15-minute lecture with equal time for discussion. Together with the high quality and focused interest of the lectures, the discussion periods were the outstanding achievement of this meeting. The limited size of the group and the common thread of interest stimulated collegial discussions that are remembered as the high point of the symposium.

The 'little brain' was discussed at multiple levels of organization for specialized regions of the digestive system. This included exciting new data for specialized regions such as the corpus and antrum of the stomach, the gall bladder and the rectum using intracellular recording of the electrical and synaptic behaviour of neurones that comprise the enteric circuits. The relative excitability of different neurones to depolarizing current injection is the standard way of classifying neurones electrophysiologically. In this respect it is apparent that there are marked regional differences in the organization of enteric reflexes. The AH neurone, first described in the small intestine where they account for about 40% of enteric neurones is far less common in the proximal and distal bowel and may be related to the relatively higher density of the extrinsic innervation of these regions. However, a thorny question which was discussed several times during the meeting was that of cell damage and its effect on individual neurone's ability to generate action potentials. This is especially important for understanding the significance of inexcitable neurones described as Type III throughout the enteric nervous system.

Considerable discussion was aroused by recent attempts to identify functional classes of enteric neurones. Immunohistochemical methods together with fibre tracing techniques were used to characterize longitudinal and circular muscle motor neurones in the small intestine. Both cholinergic and non-cholinergic motor neurones have been identified and associated with cell morphology and fibre projection. Other attempts to link morphology and electrophysiology were described for distal colon and ileum. Electrophysiological data on the identification of elements in the ascending and descending reflex pathways activated by distension and mucosal stroking in the small intestine were also presented.

Results of electrophysiological studies together with reported organ-bath pharmacological data added to insights into the mechanism of action of opiates and serotonin and substituted benzamides. These presentations clarified the localization of three subtypes of

*Address for correspondence*
David Grundy, Department of Biomedical Science, The University, Sheffield S10 2TN, UK or Jackie D. Wood, Department of Physiology, The Ohio State University College of Medicine, Columbus, Ohio, USA 43210.

5-HT receptors on gut neurones and their putative involvement in the neurophysiology of the microcircuits. The use of anti-idiotypic antibodies to 5-HT are proving especially valuable tools in this direction and their use for identifying the functional role of 5-HT on small intestinal myenteric neurones was presented.

A role for 5-HT released from enterochromaffin cells in the activation of intrinsic and extrinsic afferent fibres was also discussed. The sensitivity of extrinsic afferents to 5-HT appears to be restricted to vagal mucosal fibres which also respond to a range of other chemical mediators. Their activation by cholecystokinin was also considered and it was proposed that extrinsic reflexes evoked by cholecystokinin could account for several of its physiological actions. However, a pre-synaptic action of cholecystokinin, together with noradrenaline, on cholinergic transmission within gall bladder ganglia was described. Indeed, in the conscious animal the action of cholecystokinin on gall-bladder emptying was demonstrated to be mediated by a cholinergic pathway.

The talks on the 'big brain' included accounts of central influences on GI effector systems and the neurotransmitter involvement in information transfer between the different brain regions that influence the GI tract. This work related to the consequences of psychological stress on GI function and the potential of abnormalities in motor behaviour. Previous undescribed involvement of the brain in the determination of gall bladder function was discussed, as was the neurophysiological basis for transmission of information at the synaptic interface between the big and little brains. This latter study described a myenteric plexus preparation of gastric corpus in which the vagal innervation was preserved. The aim was to characterize the synaptic input from the vagus to so called myenteric 'command neurones'. These are proposed to play a pivotal role in the activation of enteric microcircuits by vagal signals but unexpectedly the vast majority of neurones received vagal synaptic input.

At the level of the neuro-effector junction a number of potential mediators in a number of different tissues including canine small intestinal muscularis mucosae, canine circular muscle, guinea-pig stomach and human colon were considered. A recurring theme was the relative role of vasoactive intestinal polypeptide (VIP) and nitric oxide (NO) in NANC mediated inhibitory junction potentials and relaxation. Using NO synthesis blockers and VIP antisera it appears that a role for both exists but the dominant mediator is both species and tissue specific.

Finally new insights into neural involvement in gut pathophysiology were exposed during the meeting. The basis of abnormalities of motility and secretion that occur in response to ionizing radiation were discussed as was the recovery of nervous function following surgical resection of the gut. The gut as a model for neuro-immune interactions was included in this aspect of the symposium. Responses to inflammatory mediators may involve sensory neurones. However, actions on neurones in the prevertebral and myenteric ganglia were also described at this meeting. Neuro-immune interactions that result in significant alterations in gut function in response, for example, to intestinal parasites or food antigens are an exciting new frontier that will undoubtedly grow in prominence and interest in the next few years. This in concert with presentations on the pathophysiological changes associated with inflammatory bowel disease pointed to many of the new directions for research that emerged from a highly successful symposium.